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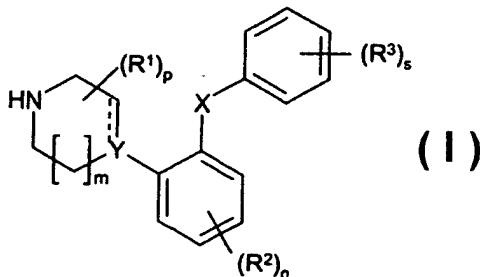
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(54) Title: PHENYL-PIPERAZINE DERIVATIVES AS SEROTONIN REUPTAKE INHIBITORS



(57) Abstract: The invention provides compounds represented by the general formula I wherein the substituents are defined in the application. The compounds are useful in the treatment of an affective disorder, including depression, anxiety disorders including general anxiety disorder and panic disorder and obsessive compulsive disorder.

WO 03/029232 A1

Phenyl-piperazine derivatives as serotonin reuptake inhibitors

The present invention relates to novel compounds which are serotonin reuptake inhibitors and as such effective in the treatment of for example depression and
5 anxiety.

Background of the invention

Selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) have become
10 first choice therapeutics in the treatment of depression, certain forms of anxiety and social phobias, because they are effective, well tolerated and have a favourable safety profile compared to the classic tricyclic antidepressants.

However, clinical studies on depression indicate that non-response to SSRIs is
15 substantial, up to 30%. Another, often neglected, factor in antidepressant treatment is compliance, which has a rather profound effect on the patient's motivation to continue pharmacotherapy.

First of all, there is the delay in therapeutic effect of SSRIs. Sometimes symptoms
20 even worsen during the first weeks of treatment. Secondly, sexual dysfunction is a side effect common to all SSRIs. Without addressing these problems, real progress in the pharmacotherapy of depression and anxiety disorders is not likely to happen.

In order to cope with non-response, psychiatrists sometimes make use of
25 augmentation strategies. Augmentation of antidepressant therapy may be accomplished through the co-administration of mood stabilizers such as lithium carbonate or triiodothyronine or by the use of electroshock.

The effect of combined administration of a compound that inhibits serotonin reuptake
30 and a 5-HT_{1A} receptor antagonist has been evaluated in several studies (Innis et al.
Eur. J. Pharmacol. 1987, 143, 1095-204 and Gartside *Br. J. Pharmacol.* 1995, 115,
1064-1070, Blier et al. *Trends in Pharmacol. Science* 1994, 15, 220). In these studies, it was found that 5-HT_{1A} receptor antagonists would abolish the initial brake on 5-HT

neurotransmission induced by the serotonin reuptake inhibitors and thus produce an immediate boost of 5-HT transmission and a rapid onset of therapeutic action.

Several patent applications have been filed, which cover the use of a combination of a 5-HT_{1A} antagonist and a serotonin reuptake inhibitor for the treatment of depression (see e.g. EP-A2-687472 and EP-A2-714663).

Another approach to increase terminal 5-HT would be through blockade of the 5-HT_{1B} autoreceptor. Microdialysis experiments in rats have indeed shown that increase of hippocampal 5-HT by citalopram is potentiated by GMC 2-29, an experimental 5-HT_{1B} receptor antagonist.

Several patent applications covering the combination of an SSRI and a 5-HT_{1B} antagonist or partial agonist have also been filed (WO 97/28141, WO 96/03400, EP-A-701819 and WO 99/13877).

It has previously been found that the combination of a serotonin reuptake inhibitor with a compound having 5-HT_{2C} antagonistic or inverse agonistic effect (compounds having a negative efficacy at the 5-HT_{2C} receptor) provides a considerable increase in the level of 5-HT in terminal areas, as measured in microdialysis experiments (WO 01/41701). This would imply a shorter onset of antidepressant effect in the clinic and an augmentation or potentiation of the therapeutic effect of the serotonin reuptake inhibitor (SRI).

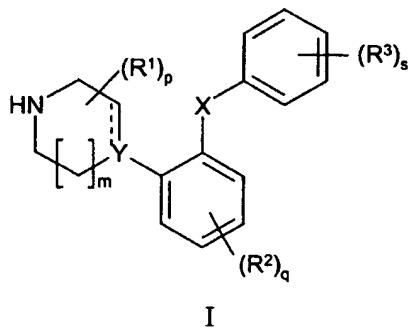
The present invention provides compounds which are serotonin reuptake inhibitors for the treatment of affective disorders such as depression, anxiety disorders including general anxiety disorder and panic disorder and obsessive compulsive disorder. Some of the compounds also have a combined effect of serotonin reuptake inhibition and 5-HT_{2C} receptor modulation, which according to WO01/41701 would imply a faster onset of anti-depressant activity.

A few of the compounds embraced by the present invention have previously been described in WO 01/49681 and in WO02/59108 However, the compounds of

WO01/49681 are not disclosed as having any therapeutic or biological activity. The compounds of WO02/59108 are disclosed as intermediates in the synthesis of compounds different from the compounds of the present invention with a therapeutic activity as melanocortin receptor agonists. One compound, 1-(2-phenoxyphenyl)-
5 piperazine, embraced by the present invention, is disclosed in US 4,064,245 as being useful in the treatment of metabolic disorders.

Summary of the invention

- 10 The present invention provides compounds of the general formula I



wherein

- 15 Y is N, C or CH;
 X represent O or S;
 m is 1 or 2;
 p is 0, 1, 2, 3, 4, 5, 6, 7 or 8;
 q is 0, 1, 2, 3 or 4;
 20 s is 0, 1, 2, 3, 4 or 5;

The dotted line represents an optional bond;

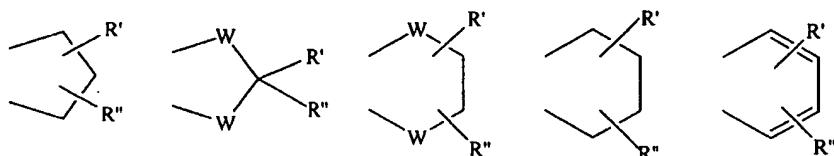
- Each R¹ is independently selected from the group represented by C₁₋₆-alkyl, or two R¹
 25 attached to the same carbon atom may form a 3-6-membered spiro-attached cyclo-alkyl;

Each R² is independently selected from the groups represented by halogen, cyano, nitro, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yloxy, C₁₋₆-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yloxy, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, acyl, C₁₋₆-alk(en/yn)yloxycarbonyl, C₁₋₆-alk(en/yn)ylsulfonyl, or -NR^XR^Y;

Each R³ is independently selected from a group represented by halogen, cyano, nitro, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yloxy, C₁₋₆-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yloxy, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)ylsulfonyl, aryl, C₁₋₆-alk(en/yn)yloxycarbonyl, acyl, -NR^XCO-C₁₋₆-alk(en/yn)yl, CONR^XR^Y or NR^XR^Y;

or two adjacent R³ substituents together form a heterocycle fused to the phenyl ring selected from the group consisting of

15



wherein W is O or S, and R' and R'' are hydrogen or C₁₋₆-alkyl:

or two adjacent R³ substituents together form a fused heteroaromatic system containing one, two or three heteroatoms,

20

wherein each R^X and R^Y is independently selected from the group represented by hydrogen, C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, or aryl; or R^X and R^Y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

or an acid addition salt thereof.

The invention also provides compounds as above provided that the compound is not 1-(2-phenoxyphenyl)-piperazine;

- The invention also provides compounds as above provided that the compound is not
- 5 1-[2-(2-Methoxyphenoxy)phenyl]piperazine, 1-[2-(2,6-dimethoxyphenoxy)phenyl]-[1,4]-diazepane, 1-{2-[3-(dimethylamino)phenoxy]phenyl}piperazine, 1-[2-(4-methylphenoxy)phenyl]piperazine, 1-[2-(3-methylphenoxy)phenyl]piperazine, 1-[2-(3-chlorophenoxy)phenyl]piperazine , 1-[2-(3-methoxyphenoxy)phenyl]piperazine and 1-(2-phenoxyphenyl)-piperazine;

10

The invention provides a compound according to the above for use as a medicament.

- The invention provides a pharmaceutical composition comprising a compound according to the above or a pharmaceutically acceptable acid addition salt thereof and
- 15 at least one pharmaceutically acceptable carrier or diluent.

- The invention provides the use of a compound according to the above or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of affective disorders, such as depression, anxiety
- 20 disorders including general anxiety disorder and panic disorder and obsessive compulsive disorder.

- The invention provides a method for the treatment of an affective disorder, including depression, anxiety disorders including general anxiety disorder and panic disorder
- 25 and obsessive compulsive disorder in a living animal body, including a human, comprising administering a therapeutically effective amount of a compound according to the above or a pharmaceutically acceptable acid addition salt thereof.

Detailed description of the invention

30

Preferred embodiments of the invention are wherein p is 0;

Preferred embodiments of the invention are wherein m is 1 or 2;

Preferred embodiments of the invention are R² is trifluoromethyl, or C₁₋₆-alkyl;

Preferred embodiments of the invention are wherein R³ is selected from the group consisting of halogen, C₁₋₆-alkoxy, C₁₋₆-sulfanyl, C₁₋₆-alkyl, hydroxy or trifluoromethyl;

Particularly preferred embodiments of the invention are wherein the compound of the
5 invention is any of the following:

- 1-[2-(2-Trifluoromethylphenylsulfanyl)phenyl]piperazine,
- 1-[2-(4-Bromophenylsulfanyl)phenyl]piperazine,
- 1-{2-[4-(Methylsulfanyl)phenylsulfanyl]phenyl}piperazine,
- 1-[2-(4-Hydroxyphenylsulfanyl)phenyl]piperazine,
- 10 1-[2-(2,4-Dimethylphenylsulfanyl)phenyl]piperazine,
- 1-[2-(3,5-Dimethylphenylsulfanyl)phenyl]piperazine,
- 1-[2-(2,6-Dimethylphenylsulfanyl)phenyl]piperazine,
- 1-[2-(2,5-Dimethylphenylsulfanyl)phenyl]piperazine,
- 1-[2-(2-Trifluoromethylphenylsulfanyl)phenyl][1,4]diazepane,
- 15 1-[2-(3-Methylphenylsulfanyl)phenyl]-[1,4]-diazepane,
- 1-[2-(4-Butylphenoxy)phenyl]piperazine,
- 1-[2-(4-Methoxyphenoxy)phenyl]piperazine,
- 2-(4-Methylphenylsulfanyl)phenyl-1-piperazine,
- 1-[2-(4-Chlorophenylsulfanyl)phenyl]-piperazine,
- 20 1-[2-(4-Methoxyphenylsulfanyl)-4-chlorophenyl]piperazine,
- 1-[2-(4-Methoxyphenylsulfanyl)-4-methylphenyl]piperazine,
- 1-[2-(4-Methoxyphenylsulfanyl)-5-methylphenyl]piperazine,
- 1-[2-(4-Fluorophenylsulfanyl)-5-methylphenyl]piperazine,
- 1-[2-(4-Methoxyphenylsulfanyl)-5-trifluoromethylphenyl]piperazine,
- 25 1-[2-(4-Chlorophenylsulfanyl)phenyl]-3-methylpiperazine,
- 1-[2-(4-Chlorophenylsulfanyl)phenyl]-3,5-dimethylpiperazine,
- 4-[2-(4-Methylphenylsulfanyl)phenyl]-3,6-dihydro-2H-pyridine,
- 4-[2-(4-Methoxyphenylsulfanyl)phenyl]-3,6-dihydro-2H-pyridine or
- 4-[2-(4-Methylphenylsulfanyl)phenyl]piperidine
- 30 or a pharmaceutically acceptable acid addition salt thereof.

Definition of substituents

Halogen means fluoro, chloro, bromo or iodo.

5

The expression C₁₋₆-alk(en/yn)yl means a C₁₋₆-alkyl, C₂₋₆-alkenyl or a C₂₋₆-alkynyl group. The expression C₃₋₈-cycloalk(en)yl means a C₃₋₈-cycloalkyl- or cycloalkenyl group.

- 10 The term C₁₋₆ alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

- 15 Similarly, C₂₋₆ alkenyl and C₂₋₆ alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

- 20 The term C₃₋₈ cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term C₃₋₈ cycloalkenyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and including one double bond.

25

In the term C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl and C₁₋₆-alk(en/yn)yl are as defined above.

- 30 The terms C₁₋₆-alk(en/yn)yloxy, C₁₋₆ alk(en/yn)ylsulfanyl, hydroxy-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yloxy, C₁₋₆-alk(en/yn)ylsulfonyl etc. designate such groups in which the C₁₋₆-alk(en/yn)yl are as defined above.

As used herein, the term C₁₋₆-alk(en/yn)yloxycarbonyl refers to groups of the formula C₁₋₆-alk(en/yn)yl-O-CO-, wherein C₁₋₆-alk(en/yn)yl are as defined above.

As used herein, the term acyl refers to formyl, C₁₋₆-alk(en/yn)ylcarbonyl,
5 arylcarbonyl, aryl-C₁₋₆-alk(en/yn)ylcarbonyl, C₃₋₈-cycloalk(en)ylcarbonyl or a C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl-carbonyl group.

The term 3-7-membered ring optionally containing one further heteroatom as used
herein refers to ring systems such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-
10 piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolyl or pyrazolyl, all of which
may be further substituted with C₁₋₆-alkyl.

The heterocycles formed by two adjacent R³ substituents and fused to the parent ring
may together form rings such as 5-membered monocyclic rings such as 3H-1,2,3-
15 oxathiazole, 1,3,2-oxathiazole, 1,3,2-dioxazole, 3H-1,2,3-dithiazole, 1,3,2-dithiazole,
1,2,3-oxadiazole, 1,2,3-thiadiazole, 1H-1,2,3-triazole, isoxazole, oxazole, isothiazole,
thiazole, 1H-imidazole, 1H-pyrazole, 1H-pyrrole, furan or thiophene and 6-membered
monocyclic rings such as 1,2,3-oxathiazine, 1,2,4-oxathiazine, 1,2,5-oxathiazine,
1,4,2-oxathiazine, 1,4,3-oxathiazine, 1,2,3-dioxazine, 1,2,4-dioxazine, 4H-1,3,2-
20 dioxazine, 1,4,2-dioxazine, 2H-1,5,2-dioxazine, 1,2,3-dithiazine, 1,2,4-dithiazine, 4H-
1,3,2-dithiazine, 1,4,2-dithiazine, 2H-1,5,2-dithiazine, 2H-1,2,3-oxadiazine, 2H-1,2,4-
oxadiazine, 2H-1,2,5-oxadiazine, 2H-1,2,6-oxadiazine, 2H-1,3,4-oxadiazine, 2H-
1,2,3-thiadiazine, 2H-1,2,4-thiadiazine, 2H-1,2,5-thiadiazine, 2H-1,2,6-thiadiazine,
2H-1,3,4-thiadiazine, 1,2,3-triazine, 1,2,4-triazine, 2H-1,2-oxazine, 2H-1,3-oxazine,
25 2H-1,4-oxazine, 2H-1,2-thiazine, 2H-1,3-thiazine, 2H-1,4-thiazine, pyrazine,
pyridazine, pyrimidine, 4H-1,3-oxathiin, 1,4-oxathiin, 4H-1,3-dioxin, 1,4-dioxin, 4H-
1,3-dithiin, 1,4-dithiin, pyridine, 2H-pyran or 2H-thiin.

The term aryl refers to carbocyclic, aromatic systems such as phenyl and naphtyl.

30

The acid addition salts of the invention are preferably pharmaceutically acceptable
salts of the compounds of the invention formed with non-toxic acids. Exemplary of
such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic,

- bis-methylenesalicylic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-
- 5 bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and
10 the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention contain chiral centres and such compounds exist in the form of isomers (i.e. enantiomers). The invention includes all
15 such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another
20 method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization of d- or l- (tartrates, mandelates or camphorsulphonate) salts. The compounds of the present invention may also be resolved by the formation of
25 diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New
30 York (1981).

Optically active compounds can also be prepared from optically active starting materials.

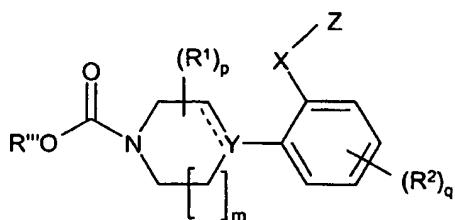
Pharmaceutical compositions

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example: Tablets may be prepared by mixing the active 5 ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are 10 compatible with the active ingredients.

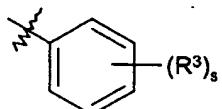
Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilising the solution and filling it in 15 suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route, for 20 example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

- 25 Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 100 mg. The total daily dose is usually in the range of about 0.05 - 500 mg, and most preferably about 0.1 to 50 mg of the active compound of the invention.
- 30 The compounds of the invention are prepared by the following general methods:
- a) Deprotection or cleavage from a polymer support of a compound with formula II



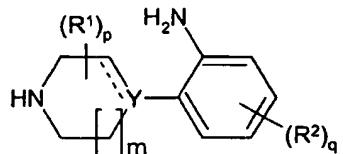
wherein Z represents



- 5 and R¹, R², R³, m, p, q, s, X, Y and the dotted line are as described above, and R^{''} is a *tert*-butyl, methyl, ethyl, allyl or benzyl group or R^{''}OCO₂ is a solid supported carbamate group, such as the Wang resin-based carbamate linker.

b) Chemical transformation of a compound with formula III

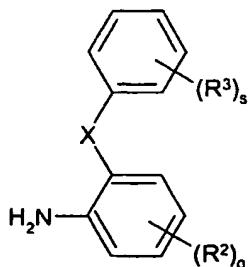
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III

- wherein R¹, R², m, p, q, Y and the dotted line are as described above, to the corresponding diazonium compound, and subsequently reacting with a compound
15 HXZ, wherein X and Z are as defined above.

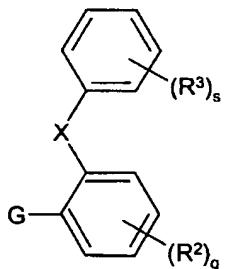
c) Reacting a compound with formula IV



IV

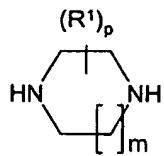
wherein R², R³, X, s and q are as described above with an alkylating agent of formula (Cl-(CH₂)_{m+1})NH(CH₂)₂Cl or (Br-(CH₂)_{m+1})NH(CH₂)₂Br wherein m are as defined above.

5 d) Reacting a compound with formula V



V

wherein R², R³, X, s and q are as described above and G is a bromine or iodine atom with a compound of formula VI



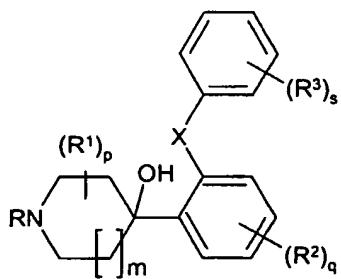
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VI

wherein R¹, m and p are as defined above.

e) Dehydrating and optionally simultaneously deprotecting a compound of formula

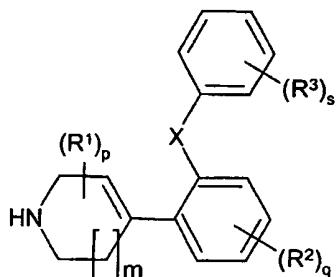
15 VII



VII

wherein R¹, R², R³, X, m, p, q and s are as described above and R is either a hydrogen atom or a BOC group.

f) Hydrogenate the double bond in a compound of formula VIII



VIII

wherein R¹, R², R³, X, m, p, q and s are as described above.

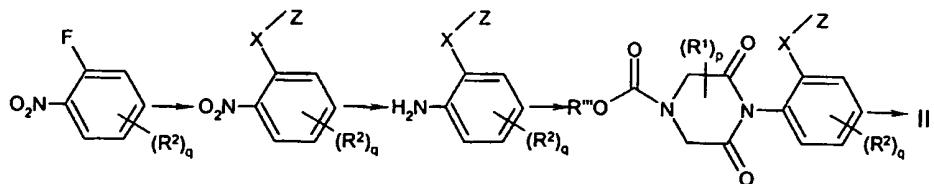
5

The deprotection according to method a) was performed by standard techniques, known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis* T.W.Greene and P.G.M. Wuts, Wiley Interscience, (1991) ISBN 0471623016.

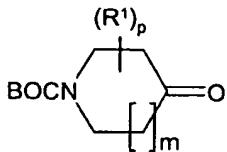
10

Starting materials of formula II wherein R''' = *tert*-Bu were prepared according to the procedure as outlined below. Fluoronitrobenzene derivatives were reacted with phenols or thiophenols according to the procedure of Sawyer et al. *J.Org. Chem.*

- 15 1998, 63, 6338 followed by reduction using standard procedures known to the persons skilled in the art. This includes reduction to the corresponding aniline using a metal hydride salt such as sodium borohydride in conjunction with palladium on carbon catalyst in an alcoholic solvent or reduction using a metal chloride salt such as zinc chloride or tin chloride. The resulting aniline was then converted to a properly substituted 3,5-diketopiperazine in a modification of the procedure of Kruse et al.
- 20 *Recl.Trav.Chim.Pays-Bas* 1998, 107, 303 using *N*-butyloxycarbonyliminodiacetic acid. The 3,5-diketopiperazine derivative was then reduced with for example borane to the corresponding BOC protected piperazine, which was then deprotected to the piperazine *in situ*.



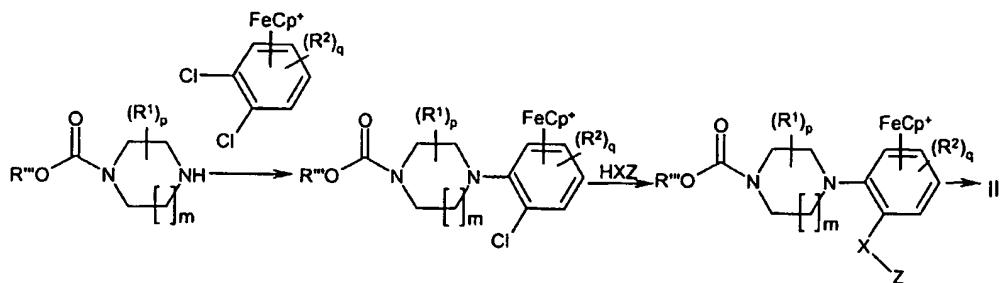
The compounds shown in formula II, wherein Y=CH and the optional double bond is reduced, were prepared from their tertiary alcohol precursors VII wherein R is a BOC group, by a modified Barton reduction in a similar manner as described in Hansen et al. *Synthesis* 1999, 1925-1930. The intermediate tertiary alcohols were prepared from 5 the corresponding properly substituted 1-bromo-phenylsulfanylbenzenes or their corresponding ethers by metal-halogen exchange followed by addition of an appropriate electrophile of the formula IX in a similar manner as described in Palmer et al. *J. Med. Chem.* 1997, 40, 1982-1989. The properly substituted 1-bromo-phenylsulfanylbenzenes were prepared in a similar manner as described in the literature by reaction of properly substituted thiophenols with properly substituted 10 aryliodides according to Schopfer and Schlapbach *Tetrahedron* 2001, 57, 3069-3073 Bates et al., *Org. Lett.* 2002, 4, 2803-2806 and Kwong et al. *Org. Lett.* 2002, 4, (in press). The corresponding substituted 1-bromo-phenoxybenzenes may be prepared as described by Buck et al. *Org. Lett.* 2002, 4, 1623-1626.



IX

The cleavage from a polymer support, such as from the Wang resin based carbamate linker, according to method a) was performed according to literature known procedures (Zaragoza *Tetrahedron Lett.* 1995, 36, 8677-8678 and Conti et al.
20 *Tetrahedron Lett.* 1997, 38, 2915-2918).

The starting material of formula II may also be prepared according to the methods described in patent application WO 01/49681. The diamines were either commercially available or synthesised by methods known to chemists skilled in the art. Iron-
25 complexes, like η^6 -1,2-dichlorobenzene- η^5 -cyclopentadienyliron(II) hexafluorophosphate and substituted analogues were synthesised according to literature known procedures (Pearson et al. *J. Org. Chem.* 1996, 61, 1297-1305) or synthesised by methods known to chemists skilled in the art.



The diazotation followed by reaction with a compound HXZ according to the method b) was performed by addition of the diazonium salt of the corresponding aniline to a 5 solution of sodium salt of a thiophenol or a phenol in an aqueous suspension of copper. The starting material of formula III was prepared as outlined in the following. A fluoronitrobenzene derivative was reacted with a piperazine derivative in a solvent such as DMF, NMP or other dipolar aprotic solvent containing an organic base such as triethylamine to afford the orthonitrophenylpiperazine derivative. The intermediate 10 orthonitrophenylpiperazine was subsequently reduced using standard procedures as stated above to give the starting material of formula III.

The reaction of a compound of formula IV with an alkylating agent of formula $(Cl-(CH_2)_{m+1})NH(CH_2)_2Cl$ or $(Br-(CH_2)_{m+1})NH(CH_2)_2Br$ as its hydrobromide or 15 hydrochloride salt, wherein m is as defined above was performed in a similar manner as described in Sircar et al. *J. Med. Chem.* 1992, 35, 4442-4449. Starting materials of formula IV were prepared as described above for starting materials of formula II.

The reaction of a compound of formula V with a diamine of formula VI in method d) 20 was performed in a similar manner as described in Nishiyama et al. *Tetrahedron Lett.* 1998, 39, 617-620. The starting material of formula V was prepared in a similar manner as described in Schopfer et al. *Tetrahedron* 2001, 57, 3069-3073.

The dehydration reaction and optional simultaneous deprotection of a compound of 25 formula VII in method e) was performed in a similar manner as described in Palmer et al *J. Med. Chem.* 1997, 40, 1982-1989. The starting material of formula VII wherein $R=H$ was prepared from a compound of formula VII wherein R is a BOC group (see above) by deprotection with hydrochloric acid in methanol. Compounds of formula

VII wherein R = BOC, may be prepared as described in Palmer et al. *J. Med. Chem.* 1997, 40, 1982-1989.

The reduction of the double bond according to method f) was generally performed by 5 catalytic hydrogenation at low pressure (< 3 atm.) in a Parr apparatus, or by using reducing agents such as diborane or hydroboric derivatives as produced *in situ* from NaBH₄ in trifluoroacetic acid in inert solvents such as tetrahydrofuran (THF), dioxane, or diethyl ether. The starting material of formula VIII was prepared from II as described in method a).

10

Examples

15 Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. Column: 30 X 4.6 mm Waters Symmetry C18 column with 3.5 µm particle size; Solvent system: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.03); Method: Linear gradient elution with 90% A to 100% B in 4 min and 20 with a flow rate of 2 mL/min. Purity was determined by integration of the UV (254 nm) and ELSD trace. The retention times (RT) are expressed in minutes. Preparative LC-MS-purification was performed on the same instrument. Column: 50 X 20 mm YMC ODS-A with 5 µm particle size; Method: Linear gradient elution with 80% A to 100% B in 7 min and with a flow rate of 22.7 mL/min. Fraction collection 25 was performed by split-flow MS detection.

¹H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated methylenchloride (99.8%D), chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) 30 were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet and b = broad singlet.

For ion-exchange chromatography, the following material was used: SCX-columns (1 g) from Varian Mega Bond Elut®, Chrompack cat. No. 220776. Prior to use, the SCX-columns were pre-conditioned with 10% solution of acetic acid in methanol (3 mL). For de-complexation by irradiation, a ultaviolet light source (300 W) from 5 Philipps was used. As starting polymer supports for solid phase synthesis, Wang-resin (1.03 mmol/g, Rapp-Polymere, Tuebingen, Germany) was used.

Preparation of Intermediates

10 *η⁶-1,2-Dichlorobenzene-η⁵-cyclopentadienyliron(II) hexafluorophosphate*
Ferrocene (167 g), anhydrous aluminium trichloride (238 g) and powdered aluminium (24 g) were suspended in 1,2-dichlorobenzene (500 mL) and heated to 90°C in a nitrogen atmosphere for 5 h with intensive stirring. The mixture was cooled to room temperature and water (1000 mL) was added carefully in small portions while cooling
15 on an ice bath. Heptane (500 mL) and diethylether (500 mL) were added, and the mixture was stirred at room temperature for 30 minutes. The mixture was extracted with diethylether (3 x 300 mL). The aqueous phase was filtered, and aqueous ammonium hexafluorophosphate (60 g in 50 mL water) was added in small portions under stirring. The product was allowed to precipitate at room temperature. After 3
20 hours the precipitate was filtered off, washed intensively with water and dried *in vacuo* (50 °C) to give 81 g (21%) of the title compound as a light yellow powder. ¹H NMR (D₆-DMSO): 5.29 (s, 5H); 6.48 (m, 2H); 7.07 (m, 2H).

Preparation of polystyrene-bound amines

25 *4-[(Piperazin-1-yl)carbonyloxymethyl]phenoxyethyl polystyrene*
4-[(4-Nitrophenoxy)carbonyloxymethyl]phenoxyethyl polystyrene (267 g, 235 mmol) was suspended in dry N,N-dimethylformamide (2 L). N-Methylmorpholine (238.0 g, 2.35 mol) and piperazine (102.0 g, 1.17 mol) were added and the mixture was stirred at room temperature for 16 h. The resin was filtered off and washed with
30 N,N-dimethylformamide (2 X 1 L), tetrahydrofuran (2 X 1 L), water (1 X 500 mL), methanol (2 X 1 L), tetrahydrofuran (2 X 1 L) and methanol (1 X 1 L). Finally, the resin was washed with dichloromethane (3 X 500 mL) and dried *in vacuo* (25 °C, 36 h) to yield an almost colourless resin (240.0 g).

The following polystyrene bound diamines were prepared analogously:

4-[{(1,4-Diazepan-1-yl)carbonyloxymethyl]phenoxyethyl polystyrene}

Preparation of resin-bound η^6 -aryl- η^5 -cyclopentadienyliron(II)

5 **hexafluorophosphates**

4-({4-[η^6 -(2-Chlorophenyl)- η^5 -cyclopentadienyliron(II)]piperazin-1-yl}carbonyloxymethyl)phenoxyethyl polystyrene hexafluorophosphate (Intermediate for 1a-1h and 1k-1l)

10 *4-[(Piperazin-1-yl)carbonyloxymethyl]phenoxyethyl polystyrene* (115.1 g, 92 mmol) was suspended in dry tetrahydrofuran (1.6 L), and η^6 -1,2-dichlorobenzene- η^5 -cyclopentadienyliron(II) hexafluorophosphate (76.0 g, 184 mmol) was added followed by potassium carbonate (50.9 g, 368 mmol). The reaction mixture was stirred at 60 °C for 16 h. After cooling to room temperature, the resin was filtered off and washed with tetrahydrofuran (2 X 500 mL), water (2 X 250 mL), tetrahydrofuran (2 X 500 mL), water (2 X 250 mL), methanol (2 X 250 mL), dichloromethane (2 X 250 mL) and methanol (2 X 250 mL). Finally, the resin was washed with dichloromethane (3 X 500 mL) and dried *in vacuo* (25 °C, 36 h) to yield a dark orange resin (142 g).

20 The following polystyrene bound iron-complex was prepared analogously:

4-({4-[η^6 -(2-Chloro-phenyl)- η^5 -cyclopentadienyliron(II)]-[1,4]-diazepan-1-yl}carbonyloxymethyl)phenoxyethyl polystyrene hexafluorophosphate (Intermediate for 1i and 1j)

25 **Preparation of further intermediates**

1-tert-Butoxycarbonyl-4-[2-(4-methylphenylsulfanyl)phenyl]piperidin-4-ol

A solution of BuLi (2.5 M in hexane, 12.0 ml, 30 mmol) was slowly added to a stirred solution of 1-bromo-2-(4-methylphenylsulfanyl)benzene (30 mmol) in dry THF (75

30 ml) under Argon at -78 °C. The solution was stirred for 10 min before 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (5.98 g, 30 mmol) was added in one portion. The solution was allowed to warm up to room temperature and then stirred for 3 h. Saturated aqueous NH₄Cl (150 ml) was added and the solution was extracted

with ethylacetate (150 ml). The organic phase was washed with brine, dried (MgSO_4) and the solvent was evaporated *in vacuo*. Crude 1 was purified by flash chromatography on silica gel (eluent: Ethylacetat/heptane 20:80) to produce the target compound as a white foam. LC/MS (m/z) 399.3 (MH^+); RT = 3.82; purity (UV, 5 ELSD): 98%, 100%; yield: 5.02 g (42%).

*1-tert-Butyloxycarbonyl-4-[2-(4-methylphenylsulfanyl)phenyl]-3,5-dioxopiperazine
(Intermediate for 2a)*

2-(4-Methylphenylsulfanyl)aniline (2.9 g, 13.5 mmol) was dissolved in dry THF (200 10 mL) and placed under a nitrogen atmosphere. N-(*tert*-butyloxycarbonyl)iminodiacetic acid (4.7 g, 20.2 mmol) and carbonyl diimidazole (4.2 g, 40.4 mmol) were added to the solution and the reaction was refluxed for 60 hours. The reaction mixture was cooled to room temperature and ethyl acetate (500 mL) was added. The resulting solution was then washed with 2 N NaHCO_3 (2 X 200 mL), 2 N HCl (2 X 200 mL) 15 and saturated sodium chloride solution (100 mL) and the solvents evaporated *in vacuo*. Yield 6.0g , 107%, ^1H NMR (CDCl_3) 1.5 (s, 9H); 2.32 (s, 3H); 4.4-4.6 (m, 4H); 7.02-7.18 (m, 3H); 7.2-7.45 (m, 5H).

The following 3,5 diketopiperazine derivatives were prepared in an analogous 20 fashion:

*1-tert-Butyloxycarbonyl-4-[2-(4-chlorophenylsulfanyl)phenyl]-3,5-dioxopiperazine
(Intermediate for 2b)*

1-tert-Butyloxycarbonyl-4-[2-(4-methoxyphenylsulfanyl)-4-chlorophenyl]-3,5-dioxopiperazine (Intermediate for 2c)

1-tert-Butyloxycarbonyl-4-[2-(4-methoxyphenylsulfanyl)-4-methylphenyl]-3,5-dioxopiperazine (Intermediate for 2d)

1-tert-Butyloxycarbonyl-4-[2-(4-methoxyphenylsulfanyl)-5-methylphenyl]-3,5-dioxopiperazine (Intermediate for 2e)

30 1-tert-Butyloxycarbonyl-4-[2-(4-fluorophenylsulfanyl)-5-methylphenyl]-3,5-dioxopiperazine (Intermediate for 2f)

1-tert-Butyloxycarbonyl-4-[2-(4-methoxyphenylsulfanyl)-5-trifluoromethylphenyl]-3,5-dioxopiperazine (Intermediate for 2g)

2-(3-Methylpiperazin-1-yl)phenylamine (intermediate for 3a)

Fluoronitrobenzene (7.1 g, 50 mmol) was dissolved in DMF (100 mL) containing triethylamine (10 g, 100 mmol) and placed under a nitrogen atmosphere. To the 5 solution was added 2-methyl-piperazine (5.5 g, 55 mmol). The reaction was heated to 80 °C for 16 hours. The reaction was allowed to cool to room temperature before the solvent was reduced to half volume *in vacuo*. Ethyl acetate (200 mL) and ice-water (250 mL) were added to the solution and the product was extracted with diethyether (2 X 200 mL). The aqueous phase was saturated with sodium chloride and extracted 10 with ethyl acetate (2 X 200 mL). The organic phases were combined, washed with saturated brine, dried over magnesium sulfate, filtered and the filtrate was concentrated *in vacuo*. The product (10.5 g) was dissolved in ethanol (250 mL). Palladium on charcoal catalyst (10% w/w, 2.2 g) was added to the solution and the 15 solution was hydrogenated in a Parr apparatus at 3 bar for 3 hours. The solution was filtered and the solvents evaporated *in vacuo* to give the aniline product. Yield (8.0 g, 83%)

The following intermediates were prepared in an analogous fashion:

2-(3,5-Dimethylpiperazin-1-yl)phenylamine (intermediate for 3b)

20

Compounds of the invention:**Example 1***1a, 1-[2-(2-Trifluoromethylphenylsulfanyl)phenyl]piperazine*

To a solution of 2-trifluoromethylthiophenol (1.75 g, 9.8 mmol) in a 1:1 mixture of tetrahydrofuran/dimethylformamide (30 mL), sodium hydride (7.4 mmol, 60% in mineral oil) was carefully added at room temperature (Caution: Generation of 25 hydrogen). The mixture was stirred for an additional 30 min after the generation of hydrogen had ceased. Subsequently, 4-($\{\eta^6\text{-}(2\text{-chlorophenyl})\text{-}\eta^5\text{-cyclopentadienyliron(II)}\}$ piperazin-1-yl}carbonyloxymethyl)phenoxyethyl polystyrene hexafluorophosphate (3.5 g, 2.45 mmol) was added and the mixture was stirred at 55 °C for 12 h. After cooling to room temperature, the resin was filtered off 30 and washed with tetrahydrofuran (2 X 50 mL), tetrahydrofuran/water (1:1) (2 X 50

mL), N,N-dimethylformamide (2 X 50 mL), water (2 X 50 mL), methanol (3 X 50 mL), tetrahydrofuran (3 X 50 mL), and subsequently with methanol and tetrahydrofuran (each 50 mL, 5 cycles). Finally, the resin was washed with dichloromethane (3 X 50 mL) and dried *in vacuo* (25 °C, 12 h) to yield a dark orange resin. The thus obtained resin and a 0.5 M solution of 1,10-phenanthroline in 3:1 mixture of pyridine/water (20 mL) was placed in light-transparent reactor tube. The suspension was agitated by rotation under irradiation with visible light for 12 h. The resin was filtered and washed with methanol (2 X 25 mL), water (2 X 25 mL) and tetrahydrofuran (3 X 25 mL) until the washing solutions were colourless (approx. 5 cycles) and the irradiation procedure was repeated until decomplexation was complete (approx. 5 cycles). After the decomplexation was completed, the resin was washed with dichloromethane (3 X 25 mL) and dried *in vacuo* (25 °C, 12 h) to obtain a light brown resin. 100 mg (77 µmol) of the thus obtained resin were suspended in a 1:1 mixture of trifluoroacetic acid and dichloromethane (2 mL) and stirred at room temperature for 2 h. The resin was filtered off and washed with methanol (1 X 0.5 mL) and dichloromethane (1 X 0.5 mL). The filtrates were collected and the volatile solvents evaporated *in vacuo*. The crude product was purified by preparative LC-MS and subsequently by ion-exchange chromatography. LC/MS (m/z) 339 (MH⁺); RT = 2.39; purity (UV, ELSD): 92%, 100%; overall yield: 1 mg (4%).

20

The following arylpiperazines and aryl[1,4]diazepanes were prepared analogously:

1b, *1-[2-(4-Bromophenylsulfanyl)phenyl]piperazine*: LC/MS (m/z) 350 (MH⁺); RT = 2.46; purity (UV, ELSD): 75%, 92%; yield: 2 mg (7%).

1c, *1-[2-(Methylsulfanyl)phenylsulfanyl]phenyl]piperazine*: LC/MS (m/z) 317 (MH⁺); RT = 2.39; purity (UV, ELSD): 91%, 100%; yield: 2 mg (8%).

1d, *1-[2-(4-Hydroxyphenylsulfanyl)phenyl]piperazine*: LC/MS (m/z) 287 (MH⁺); RT = 1.83; purity (UV, ELSD): 84%, 100%; yield: 3 mg (13%).

1e, *1-[2-(2,4-Dimethylphenylsulfanyl)phenyl]piperazine*: LC/MS (m/z) 299 (MH⁺); RT = 2.48; purity (UV, ELSD): 95%, 100%; yield: 4 mg (17%).

1f, *1-[2-(3,5-Dimethylphenylsulfanyl)phenyl]piperazine*: LC/MS (m/z) 299 (MH⁺); RT = 2.51; purity (UV, ELSD): 96%, 100%; yield: 5 mg (21%).

1g, *1-[2-(2,6-Dimethylphenylsulfanyl)phenyl]piperazine*: LC/MS (m/z) 299 (MH⁺); RT = 2.42; purity (UV, ELSD): 97%, 100%; yield: 4 mg (17%).

- 1h, 1-[2-(2,5-Dimethylphenylsulfanyl)phenyl]piperazine:** LC/MS (m/z) 299 (MH^+); RT = 2.46; purity (UV, ELSD): 97%, 100%; yield: 1 mg (4%).
- 1i, 1-[2-(2-Trifluoromethylphenylsulfanyl)phenyl]-[1,4]-diazepane:** LC/MS (m/z) 353 (MH^+); RT = 2.46; purity (UV, ELSD): 70%, 96%; yield: 1 mg (4%).
- 5 **1j, 1-[2-(3-Methylphenylsulfanyl)phenyl]-[1,4]-diazepane:** LC/MS (m/z) 299 (MH^+); RT = 2.44; purity (UV, ELSD): 76%, 93%; yield: 1 mg (4%).
- 1k, 1-[2-(4-Butylphenoxy)phenyl]piperazine:** LC/MS (m/z) 311 (MH^+); RT = 2.77; purity (UV, ELSD): 91%, 100%; yield: 4 mg (17%).
- 10 **1l, 1-[2-(4-Methoxyphenoxy)phenyl]piperazine:** LC/MS (m/z) 285 (MH^+); RT = 2.08; purity (UV, ELSD): 93%, 100%; yield: 4 mg (18%)

Example 2

- 2a, 2-(4-Methylphenylsulfanyl)phenyl-1-piperazine hydrochloride**
1-*tert*-Butyloxycarbonyl-4-[2-(4-methylphenylsulfanyl)phenyl]-3,5-dioxo-piperazine
15 (5.5 g, 13 mmol) was dissolved in dry THF (50 mL) and placed under a nitrogen atmosphere. Borane tetrahydrofuran complex (50 mmol, 1.0 M) in tetrahydrofuran was added and the reaction was refluxed for ten minutes. Excess borane was quenched by the addition of an excess of ethyl acetate and the reaction was refluxed for a further 20 minutes. The reaction was allowed to cool to room temperature before
20 hydrogen chloride dissolved in methanol (50 mL, 4 M) was added and the reaction was refluxed for 4.5 hours. The reaction was allowed to cool to room temperature and the reaction was concentrated *in vacuo*. The compound was crystallised from the gum residue by the addition of ether/methanol solution. The crystalline solid was filtered and washed with ether/methanol (1:1) to give a white crystalline solid. Yield (2.0 g,
25 47%) ^1H NMR (D₆-DMSO) 2.35 (s, 3H); 3.18 (br s, 8H); 6.68 (d, 2H); 7.02 (m, 1H); 7.18 (m, 1H); 7.3-7.5 (m, 4H); MS (MH^+) 285.

The following compounds were prepared in an analogous fashion:

- 2b, 1-[2-(4-chlorophenylsulfanyl)phenyl]piperazine** LC-MS (m/z) 305.1 (MH^+) RT
30 =2.46 purity (UV, ELSD) 71%, 91% yield 0.096 g, 100%
- 2c, 1-[2-(4-methoxyphenylsulfanyl)-4-chlorophenyl]piperazine** LC-MS (m/z) (MH^+) 335.2 RT =2.38 purity (UV, ELSD) 98%, 100% yield 0.22 g, 62%

2d, 1-[2-(4-methoxyphenylsulfanyl)-4-methylphenyl]piperazine LC-MS (m/z) (MH⁺)

315.1 RT=2.33 purity (UV, ELSD) 97%, 100% yield 0.21g, 56%

2e, 1-[2-(4-methoxyphenylsulfanyl)-5-methylphenyl]piperazine LC-MS (m/z) (MH⁺)

315.2 RT=2.38 (UV, ELSD) 98%, 100% yield 2.3 g, 58%

5 **2f, 1-[2-(4-fluorophenylsulfanyl)-5-methylphenyl]piperazine LC-MS (m/z) (MH⁺)**

303.2 RT=2.46 (UV) 98% yield 2.1 g, 62%

2g, 1-[2-(4-Methoxyphenylsulfanyl)-5-trifluoromethylphenyl]piperazine LC-MS (m/z)

(MH⁺) 369 RT=2.50 (UV, ELSD) 96%, 100% yield 0.54 g, 31%

10 **Example 3**

3a, 1-[2-(4-Chlorophenylsulfanyl)phenyl]-3-methylpiperazine

2-(3-Methylpiperazin-1-yl)phenylamine (0.96 g, 5 mmol) was dissolved in 30 mL water containing sulfuric acid (0.28 mL, 5.2 mmol) and the solution was cooled to 0 °C and sodium nitrite (0.36 g, 5.2 mmol) was added. The reaction was stirred for 30 minutes before the pH of the reaction was adjusted to pH 7 with sodium acetate. The diazonium salt solution was then added dropwise to a solution of 4-chlorothiophenol in a suspension of copper (0.3 g, 5 mmol) in 2 M NaOH (4 mL). After addition, the reaction mixture was heated to 60°C for 30 minutes before being allowed to cool to room temperature and ethyl acetate (10 mL) was added. The reaction mixture was filtered and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 X 10 mL). The combined organic phases were dried (MgSO_4) and volatile solvents evaporated *in vacuo*. The crude product was purified by flash chromatography using silica gel, eluting with ethyl acetate /methanol/ammonia 96:3:1. The pure product was isolated as a colourless oil. Yield (0.18 g, 11%) ¹H NMR (CDCl_3 , 500 MHz) 1.12 (d, 3H); 2.6-2.72 (br m, 2H); 3.0-3.15 (m, 5H); 6.9 (m, 2H); 7.08 (d, 1H); 7.15 (m, 1H); 7.25-7.35 (m, 4H); MS (MH⁺) 319.1.

The following compound was prepared in an analogous fashion:

3b, 1-[2-(4-Chlorophenylsulfanyl)phenyl]-3,5-dimethylpiperazine LC-MS (m/z)

30 (MH)⁺ 333.1 RT=2.29 (UV, ELSD) 83%, 100% yield 0.54 g, 31%.

Example 4**4a, 4-[2-(4-Methylphenylsulfanyl)phenyl]-3,6-dihydro-2H-pyridine**

Concentrated aq hydrochloric acid (10 ml) was added to a stirred solution of 1-*tert*-butoxycarbonyl-4-[2-(4-methylphenylsulfanyl)phenyl]piperidin-4-ol (0.84 g, 2.1 mmol) in acetic acid (30 mL). The solution was boiled under reflux overnight, cooled to room temperature and then stirred in an ice bath. An aqueous solution of NaOH (9.1 M, 40 mL) was slowly added and the unclear solution was extracted with ethyl acetate (2 x 40 ml). The combined organic phases were dried (MgSO_4) and the solvents evaporated *in vacuo*. The crude material (0.48 g) was dissolved in ethyl acetate (3.2 mL) at 50 °C and a solution of oxalic acid (0.11 g) in EtOH (3.2 mL) was slowly added. The target compound was collected as a white oxalic salt. ^1H (DMSO- d_6) δ 7.3-7.2 (m, 7H); 7.15 (m, 1H); 7.00 (m, 1H); 5.6 (d, 1H); 3.7 (d, 2H); 3.25 (t, 2H); 2.6 (m, 2H); 2.3 (s, 3H). LC/MS (m/z) 282.2 (MH^+); RT = 2.24; purity (UV, ELSD): 99%, 100%; yield: 0.31 g (40%).

The following derivative was prepared analogously:

4b, 4-[2-(4-Methoxyphenylsulfanyl)phenyl]-3,6-dihydro-2H-pyridine

LC/MS (m/z) 298 (MH^+); RT = 2.00; purity (UV, ELSD): 97%, 100%; yield: 0.28 g (30%).

Example 5**5a, 4-[2-(4-Methylphenylsulfanyl)phenyl]piperidine**

Methyl Chloro-oxo-acetate (1.37 g, 11.25 mmol) was added to a stirred solution of 1-*tert*-butoxycarbonyl-4-[2-(4-methylphenylsulfanyl)phenyl]piperidin-4-ol (3.00 g, 7.5 mmol) and 4-(dimethylamino)pyridine (1.65 g, 13.5 mmol) in a mixture of dry CH_3CN (24 ml) and CHCl_3 (12 mL) at 0 °C under argon. The reaction mixture was allowed to reach room temperature and then stirred 2 h. Ethyl acetate (140 mL) was added and some salts were removed by filtration through celite. The organic phase was washed with sat. NaHCO_3 (140 ml), brine (140 mL) and dried (MgSO_4). The solvents were evaporated *in vacuo* and the crude material was dried *in vacuo*. This material was dissolved in dry toluen (48 mL) under argon. Bu_3SnH (3.27 g, 11.25 mmol) and AIBN (0.31 g, 1.88 mmol) were added. The solution was stirred under argon at 90 °C for 2.5 h. The solvent was evaporated *in vacuo*, and the crude material

was purified by flash chromatography on silicagel (eluent: a stepwise gradient of ethylacetat in heptane from 10:90 to 20:80) to produce 4-(2-(4-methylphenylsulfanyl)phenyl)-piperidine-1-carboxylic acid tert-butyl ester as a clear oil (1.94 g, 67%). This oil was dissolved in MeOH (9.2 mL) and HCl in diethylether 5 (2.0 M) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The target compound was collected as its hydrochloride. M.p 229-231 °C. Calculated for C₁₈H₂₁NS.HCl: C 67.58; H 6.63; N 4.38. Found: C 67.33; H 6.97; N 4.31. LC/MS (m/z) 284 (MH⁺); RT = 2.12; purity (UV, ELSD): 96%, 100%; yield: 0.26 g (46%).

10

Inhibition of the uptake of [³H]Serotonin into whole rat brain synaptosomes

The compounds were tested with respect to their 5-HT reuptake inhibiting effect by measuring their ability to inhibit the uptake of [³H]serotonin into whole rat brain synaptosomes *in vitro*. The assay was performed as described by Hyttel

15 *Psychopharmacology 1978, 60, 13.*

5-HT_{2C} receptor efficacy as determined by fluorometry

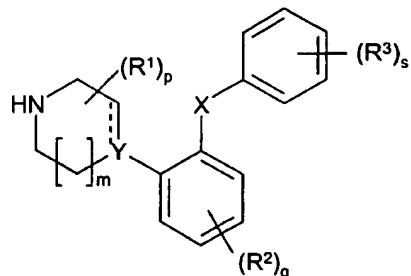
The compounds were tested with respect to their efficacy on 5-HT_{2C} receptor-expressing CHO cells (Euroscreen) as determined by fluorometric imaging plate reader (FLIPR) analysis. This assay was carried out according to Molecular Devices Inc. instructions for their FLIPR Calcium Assay Kit and as modified from Porter et al. *British Journal of Pharmacology 1999, 128, 13.*

Preferred compounds of the present invention exhibit serotonin reuptake inhibition 25 below 200 nM (IC₅₀) in the assay above. More preferred are the compounds which exhibit inhibition below 100 nM and most preferably below 50 nM. Compounds of particular interest exhibit serotonin reuptake inhibition below 10nM;

30

Claims:

1. A compound represented by the general formula I



5

I

wherein

Y is N, C or CH;

X represent O or S;

10 **m** is 1 or 2;

p is 0,1, 2, 3, 4, 5, 6, 7 or 8;

q is 0, 1, 2, 3 or 4;

s is 0, 1, 2, 3, 4 or 5;

15 The dotted line represents an optional bond;

Each **R¹** is independently selected from the group represented by C₁₋₆-alkyl, or two R¹ attached to the same carbon atom may form a 3-6-membered spiro-attached cycloalkyl;

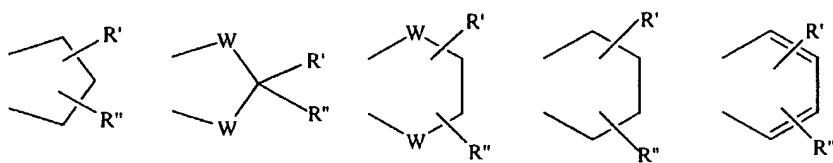
20

Each **R²** is independently selected from the groups represented by halogen, cyano, nitro, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yloxy, C₁₋₆-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yloxy, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, acyl, C₁₋₆-

25 alk(en/yn)yloxycarbonyl, C₁₋₆-alk(en/yn)ylsulfonyl, or -NR^XR^Y; -NR^XCO-C₁₋₆-alk(en/yn)yl;

Each R³ is independently selected from a group represented by halogen, cyano, nitro, C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)yloxy, C₁₋₆-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yl, halo-C₁₋₆-alk(en/yn)yloxy, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, C₁₋₆-alk(en/yn)ylsulfonyl, aryl, 5 C₁₋₆-alk(en/yn)yloxycarbonyl, acyl, -NR^XCO-C₁₋₆-alk(en/yn)yl, -CONR^XR^Y or NR^XR^Y;

or two adjacent R³ substituents together form a heterocycle fused to the phenyl ring selected from the group consisting of



10

wherein W is O or S, and R' and R'' are hydrogen or C₁₋₆-alkyl:

or two adjacent R³ substituents together form a fused heteroaromatic system containing one, two or three heteroatoms,

15 wherein each R^X and R^Y is independently selected from the group represented by hydrogen, C₁₋₆-alk(en/yn)yl, C₃₋₈-cycloalk(en)yl, C₃₋₈-cycloalk(en)yl-C₁₋₆-alk(en/yn)yl, or aryl; or R^X and R^Y together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;
20 or a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to claim 1, provided that the compound is not 1-(2-phenoxyphenyl)piperazine

25 3. A compound according to claim 1, provided that the compound is not 1-[2-(2-Methoxyphenoxy)phenyl]piperazine, 1-[2-(2,6-dimethoxyphenoxy)phenyl]-[1,4]-diazepane, 1-{2-[3-(dimethylamino)phenoxy]phenyl}piperazine, 1-[2-(4-methylphenoxy)phenyl]piperazine, 1-[2-(3-methylphenoxy)phenyl]piperazine, 1-[2-(3-chlorophenoxy)phenyl]piperazine, 1-[2-(3-methoxyphenoxy)phenyl]piperazine and
30 1-(2-phenoxyphenyl)-piperazine;

4. The compound according to any of the claims 1-3, wherein p is 0, 1 or 2.
5. The compound according to any of the claims 1-4, wherein R¹ is C₁₋₆-alkyl.
- 5 6. The compound according to any of the claims 1-5, wherein m is 1 or 2.
7. The compound according to any of the claims 1-6, wherein q is 0, 1 or 2.
8. The compound according to any of the claims 1-7, wherein R² is trifluoromethyl, or
10 C₁₋₆- alkyl.
9. The compound according to any of the claims 1-8, wherein s is 1 or 2.
10. The compound according to any of the claims 1-9 wherein R³ is selected from the
15 group consisting of halogen, C₁₋₆-alkoxy, C₁₋₆-sulfanyl, C₁₋₆- alkyl, hydroxy or trifluoromethyl.
11. The compound according to any of the above claims, said compound being
1-[2-(2-Trifluoromethylphenylsulfanyl)phenyl]piperazine,
20 1-[2-(4-Bromophenylsulfanyl)phenyl]piperazine,
1-{2-[4-(Methylsulfanyl)phenylsulfanyl]phenyl}piperazine,
1-[2-(4-Hydroxyphenylsulfanyl)phenyl]piperazine,
1-[2-(2,4-Dimethylphenylsulfanyl)phenyl]piperazine,
1-[2-(3,5-Dimethylphenylsulfanyl)phenyl]piperazine,
25 1-[2-(2,6-Dimethylphenylsulfanyl)phenyl]piperazine,
1-[2-(2,5-Dimethylphenylsulfanyl)phenyl]piperazine,
1-[2-(2-Trifluoromethylphenylsulfanyl)phenyl][1,4]diazepane,
1-[2-(3-Methylphenylsulfanyl)phenyl]-[1,4]-diazepane,
1-[2-(4-Butylphenoxy)phenyl]piperazine,
30 1-[2-(4-Methoxyphenoxy)phenyl]piperazine,
2-(4-Methylphenylsulfanyl)phenyl-1-piperazine,
1-[2-(4-Chlorophenylsulfanyl)phenyl]-piperazine,
1-[2-(4-Methoxyphenylsulfanyl)-4-chlorophenyl]piperazine,

- 1-[2-(4-Methoxyphenylsulfanyl)-4-methylphenyl]piperazine,
1-[2-(4-Methoxyphenylsulfanyl)-5-methylphenyl]piperazine,
1-[2-(4-Fluorophenylsulfanyl)-5-methylphenyl]piperazine,
1-[2-(4-Methoxyphenylsulfanyl)-5-trifluoromethylphenyl]piperazine,
5 1-[2-(4-Chlorophenylsulfanyl)phenyl]-3-methylpiperazine,
1-[2-(4-Chlorophenylsulfanyl)phenyl]-3,5-dimethylpiperazine,
4-[2-(4-Methylphenylsulfanyl)phenyl]-3,6-dihydro-2H-pyridine,
4-[2-(4-Methoxyphenylsulfanyl)phenyl]-3,6-dihydro-2H-pyridine or
4-[2-(4-Methylphenylsulfanyl)phenyl]piperidine;

10

or a pharmaceutically acceptable acid addition salt thereof.

12. A pharmaceutical composition comprising a compound according to claims 1-
11 or a pharmaceutically acceptable acid addition salt thereof and at least one
15 pharmaceutically acceptable carrier or diluent.

13. The use of a compound according to claims 1 to 11 or a pharmaceutically
acceptable acid addition salt thereof for the preparation of a medicament for the
treatment of affective disorders, such as depression, anxiety disorders including
20 general anxiety disorder and panic disorder and obsessive compulsive disorder.

14. A method for the treatment of an affective disorder, including depression,
anxiety disorders including general anxiety disorder and panic disorder and obsessive
compulsive disorder in a living animal body, including a human, comprising
25 administering a therapeutically effective amount of a compound according to claims
1- 11 or a pharmaceutically acceptable acid addition salt thereof.

15. A compound according to claims 1-11 for use as a medicament.

INTERNATIONAL SEARCH REPORT

| |
|--------------------------------------------------|
| International application No. PCT/DK 02/00659 |
|--------------------------------------------------|

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 295/096, C07D 241/04, C07D 243/08, C07D 211/20, C07D 211/70,
A61K 31/44, A61K 31/4965, A61P 25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM. ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | GB 1489711 A (SCIENCE UNION ET CIE, SOCIETE FRANCAISE DE RECHERCHE MEDICALE), 26 October 1977 (26.10.77) -- | 1,4,6-7,12, 15 |
| P,X | WO 02059108 A1 (ELI LILLY AND COMPANY), 1 August 2002 (01.08.02), pages 107-109, compounds 32A-36A -- | 1 |
| X | EP 0755923 A1 (SUNTORY LIMITED), 29 January 1997 (29.01.97), examples 35 and 36 -- | 1 |

Further documents are listed in the continuation of Box C.

See patent family annex.

| | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| * Special categories of cited documents: | |
| "A" document defining the general state of the art which is not considered to be of particular relevance | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "E" earlier application or patent but published on or after the international filing date | "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "O" document referring to an oral disclosure, use, exhibition or other means | "&" document member of the same patent family |
| "P" document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

21 January 2003

Date of mailing of the international search report

22-01-2003

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INTERNATIONAL SEARCH REPORT

2

International application No.

PCT/DK 02/00659

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | WO 0149678 A1 (H. LUNDBECK A/S), 12 July 2001 (12.07.01), the examples, claims 1 and 13-14, page 1, lines 5-8 --- ----- | 1-15 |

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/DK02/00659**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 14
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK02/00659

Claim 14 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT
Information on patent family members

| | |
|-------------------------------|--|
| International application No. | |
| PCT/DK 02/00659 | |

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
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